

DAIDS Bethesda, MD USA	POLICY	No.: DWD-POL-SM-01.00
	Requirements for On-Site Monitoring of DAIDS Funded and/or Sponsored Clinical Trials	Page 1 of 7
	Approval Date: 20 DEC 06 Effective Date: 05 FEB 07	Replaces: V 1.0

1.0 PURPOSE

This policy defines the minimum requirements for on-site monitoring of Division of Acquired Immunodeficiency Syndrome (DAIDS) funded and/or sponsored clinical trials to ensure consistency and acceptability of the research data, safety of the participants, and compliance with all requirements.

2.0 SCOPE

This policy applies to all sites conducting DAIDS funded and/or sponsored clinical trials either within or outside of an HIV/AIDS Clinical Trials Network.

3.0 BACKGROUND

The monitoring of clinical research sites is one element of a larger program of clinical trials oversight developed by DAIDS to fulfill its responsibilities to:

- Ensure the safety and welfare of participants
- Maximize adherence in the conduct of clinical trials with applicable regulations, policies, standard procedures, required guidelines, and study protocols
- Verify data quality, completeness, and accuracy

The overall monitoring program involves careful review of proposed clinical trials, a requirement for meaningful local quality control/quality assurance programs, site performance evaluation systems, structured interim reviews of trial data, and appropriate site monitoring. Data reviews, including individual adverse event reports as well as summaries of both safety and efficacy data, necessarily presume that captured data are accurate and essentially complete. Clinical site monitoring is required to supply empirical evidence regarding that presumption.

In addition to Food and Drug Administration (FDA) regulated Investigational New Drug Application (IND) studies, DAIDS supports clinical research, that may involve approved study agents used in new indications or treatment strategies or other interventions that may involve substantial risks to participants. This relative risk, as well as the scope and complexity of the research, will influence the type and extent of monitoring required. The following criteria may be used to guide these decisions at the Program level including whether monitoring will be supplied through DAIDS, a pharmaceutical sponsor, and/or an investigator.

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4.0 DEFINITIONS

Auditing – Independent on-site quality assurance of monitoring performed at clinical research sites (including pharmacies and laboratories). Auditors must be fully distinct and independent from entities providing site monitoring services.

Monitors - For the purpose of this policy, monitors are individuals qualified by education or experience, whose primary role is to ensure compliance with the applicable regulations, policies, and standard procedures, as well as compliance with the study protocol as approved by the institutional review board or research ethics board.

- **DAIDS Monitor** - A monitor who is contracted by DAIDS.
- **External Non-DAIDS Monitor** - A qualified monitor not contracted by DAIDS and not employed or supervised by the study investigators, network, or site, has no affiliation with any of the participating clinical research sites, and has no role in trial conduct except as a site monitor. The monitor must be contracted or supplied by an organization (i.e. pharmaceutical sponsor, CRO, or academic institution) that conducts independent clinical site monitoring utilizing its own monitoring and reporting SOPs and having a distinct and independent supervisory structure for monitoring services.
- **Internal Non-DAIDS Monitor** – A qualified employee of a network involved with conduct of the clinical trial having no affiliation with any of the participating clinical research sites and not involved with the conduct of the trial at any participating clinical research site except for his/her role as a monitor.

For additional definitions, see the DAIDS glossary.

5.0 RESPONSIBILITIES

Clinical site monitors will conduct on-site review of source documents, participant records, regulatory files, facilities, laboratories and pharmacies. Detailed reports will be provided to the Principal Investigator (PI) as well as to DAIDS staff.

- The PI is ultimately responsible for the correction of deficiencies identified during a monitoring visit.
- DAIDS Program staff is responsible for reviewing monitoring reports and ensuring that the PI has a plan of action for correction of deficiencies and follows through on action items.

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6.0 POLICY

6.1 Monitoring for all DAIDS funded and/or sponsored clinical trials

6.1.1 All clinical trials for which DAIDS is the IND-holder must be monitored by a DAIDS monitor. The extent of monitoring will be related to the size, risk and complexity of the trial and may change depending upon the status of the trial, the needs of DAIDS and the performance of the site. For some trials, non-DAIDS monitoring may also be performed

6.1.2 Clinical trials for which DAIDS does not hold an IND will be monitored by a DAIDS monitor and/or by a non-DAIDS monitor.

Use of either external non-DAIDS monitoring and internal non-DAIDS monitoring must be specifically approved in writing by DAIDS. If approved, the monitors must be identified and a detailed monitoring plan approved by DAIDS prior to enrollment. If internal non-DAIDS monitoring is approved, DAIDS will also conduct site monitoring through the use of DAIDS monitors at a frequency and intensity level to be determined by DAIDS staff.

In all cases involving use of non-DAIDS monitors, DAIDS retains the option to conduct on-site monitoring and/or auditing by DAIDS monitors or auditors as needed to ensure the rights and safety of participants, integrity of trial data, and compliance with all requirements.

6.2 Minimum standards for site monitoring of clinical trials

6.2.1 Selection and Qualifications of the Clinical Site Monitor

6.2.1.1. Contract Research Organizations must use monitors who meet the qualifications set forth in their respective contracts with DAIDS, unless exceptions are specifically granted by DAIDS.

6.2.1.2. If site monitors are provided or contracted by an entity other than DAIDS (including the use of internal monitors, if approved), the SOPs and reporting procedures that are being followed, as well as the monitor(s), must be approved by DAIDS.

6.2.1.3. In general, monitors should be qualified by experience and training and will have a Bachelor's/University degree or

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equivalent in nursing, pharmacy, biology, or other biomedical sciences.

- 6.2.1.4. Monitors should have experience in clinical research, and preferably have experience in monitoring clinical trials, implementing HIV/AIDS studies, working with community and/or hospital clinic or laboratory staff, teaching clinical staff, and/or performing quality assurance audits.

Note: Exceptions to these qualifications will require review and approval from DAIDS staff.

6.2.2 Frequency of monitoring visits

- 6.2.2.1. DAIDS staff will determine the frequency of monitoring visits based on the risk, size, and complexity of the trial. IND trials will be monitored no less than twice per year and at least one of those monitoring visits will be conducted by a DAIDS monitor.
- 6.2.2.2. Non-IND trials must be monitored by a DAIDS monitor or external non-DAIDS monitor at least once a year. The frequency of monitoring visits will be determined based on risk, size and complexity of the trial.
- 6.2.2.3. The degree and frequency of monitoring will be re-assessed periodically.

6.2.3 Review of Site Regulatory Files

- 6.2.3.1. At a minimum, the regulatory file must be reviewed once per year. Please refer to DAIDS policy *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* for more details.

6.2.4 Assessment of Pharmacy Operations

- 6.2.4.1. DAIDS Pharmaceutical Affairs Branch (PAB) will determine the frequency of pharmacy visits based on the risk, size, and complexity of the trial. At a minimum, the operations of the investigational pharmacy will be assessed once per year by a DAIDS monitor.

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6.2.5 Review of Clinical Research Participant Records at Each Visit

Note: A sufficient number must be reviewed to constitute an adequate sample of the current enrollment.

- 6.2.5.1. The signed informed consent documents will be reviewed for compliance with Good Clinical Practice (GCP) and the DAIDS Policy *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*.
- 6.2.5.2. Original source documentation will be reviewed to verify all inclusion/exclusion criteria and for compliance with protocol requirements and the DAIDS policy for source documentation.
- 6.2.5.3. Individual participant's original source documents will be reviewed and compared to the protocol requirements and the completed case report forms.
- 6.2.5.4. Factors in determining what constitutes an "adequate sample" may include (but are not limited to): study risk, size, complexity, age of participants, experience of clinical research site staff, and findings from prior site monitoring visits. The number of records to be reviewed will be determined by DAIDS staff and defined in the monitoring plan.

6.2.6 Clinical Site Monitoring Visit Reports

- 6.2.6.1. Written reports of the reviews of research records, regulatory files, and site and pharmacy operations must be submitted to DAIDS by the designated monitor within the DAIDS standard timelines.
- 6.2.6.2. Prior to its distribution, information that could lead to unblinding will be removed from the report. Information that is removed from a report due to potential for unblinding, such as, but not limited to, physical inventories, is to be submitted in a separate document to DAIDS PAB.
- 6.2.6.3. Distribution of visit reports will include (but not be limited to): appropriate DAIDS staff and the Principal Investigator.

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6.2.7 Issues or Findings Requiring Expedited Reporting

- 6.2.7.1. Suspected instances of scientific misconduct will be immediately reported directly to the DAIDS Clinical Research Resources Branch (CRRB) Chief, the DAIDS Monitoring Contract Project Officer (if applicable), and Program Officer(s) responsible for the site and for the study at DAIDS.
- 6.2.7.2. Reporting of other critical issues or findings will be expedited according to the seriousness of the finding. In general, these issues/findings should be reported to DAIDS as soon as possible.

7.0 REFERENCES

U.S. Code of Federal Regulations, Title 21, Part 312.56: Review of Ongoing Investigations
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>

FDA Guideline for the Monitoring of Clinical Investigations (November 1998)
http://www.fda.gov/ora/compliance_ref/bimo/clinguid.pdf

DAIDS Policy
 Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials

DAIDS Policy
 Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS funded and/or Sponsored Clinical Trials

8.0 INQUIRIES

Questions and comments regarding this policy may be directed to:

NIAIDOPCROPOLICYGROUP@mail.nih.gov

9.0 AVAILABILITY

This policy is available electronically at the following URL:
<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Default.htm>

The signed original is maintained in the OPCRO policy office.

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10.0 CHANGE SUMMARY

Version #	Date	Replaces	Date of Revision	Rationale for Revision/Retirement
2.0	20 DEC 06	V 1.0	20 DEC 06	DAIDS Final Review
1.0	14 JUL 06	N/A	N/A	N/A

11.0 APPENDICES

None.

12.0 APPROVAL

Signature

Program/Branch

Date

Authorized By: *Richard Hafner*

December 20, 2006

Richard Hafner, MD
Director

Office for Policy in
Clinical Research
Operations (OPCRO)